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, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of he Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as riginally filed in connection with the patent application identified therein together with the tatement of inventorship and of right to grant of a Patent (Form 7/77), which was subsequently led.

accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in s certificate and any accompanying documents has re-registered under the Companies Act 80 with the same name as that with which it was registered immediately before re-registration e for the substitution as, or inclusion as, the last part of the name of the words "public limited mpany" or their equivalents in Welsh, references to the name of the company in this certificate any accompanying documents shall be treated as references to the name with which it is so egistered.

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Dated 4 December 2006

Patents Form 1/77

Patents Act 1977
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The Patent Office

31 MAY 2001

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference — PHAZ / P24567GB

31MAY01 E633380-3 D02866
P01/7700 0.00-0113129.1

2. Pate
(The — **0113129.1**

31 MAY 2001

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Pharmacore AB
c/o Projipharma AB
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Sweden

c/o A+ Science Invest AB
PO Box 3046
SE-400 10 Göteborg
Sweden

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Sweden 61571586 01

22/10/01

4. Title of the invention

PHARMACEUTICALLY-USEFUL COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
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NOTTINGHAM
NG1 5DD

Patents ADP number *(if you know it)* — **1305010**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

YES

a) *any applicant named in part 3 is not an inventor; or*
b) *there is an inventor who is not named as an applicant, or*
c) *any named applicant is a corporate body. See note (d))*

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	24
Claims*(s)*	5
Abstract	1
Drawing*(s)*	0

10. If you are also filing in any of the following, state how many against each item.

Priority Documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	NO
Request for preliminary examination and search *(Patents Form 9/77)*	NO
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Eric Potter Clarkson

Signature

ERIC POTTER CLARKSON

Date

30 May 2001

12. Name and daytime telephone number of person to contact in the United Kingdom **0115 9552211**

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

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Patents Form 7/77

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THE PATENT OFFICE
21 NOV 2001
NEWPORT

The Patent Office

7/77

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Statement of inventorship and of right to grant of a patent

1.	Your reference	PHAZ/P24567GB
2.	Patent application number *(if you know it)*	0113129.1
3.	Full name of the or of each applicant	Pharmacore AB
4.	Title of the invention	Pharmaceutically-Useful Compounds
5.	State how the applicant*(s)* derived the right from the inventor*(s)* to be granted a patent	By virtue of assignment
6.	How many, if any, additional Patents Forms 7/77 are attached to this form *(see note (c))*	None
7.		I/We believe that the person*(s)* named over the page *(and on any extra copies of this form)* is/are the inventor*(s)* of the invention which the above patent application relates to. Signature Date 20 November 2001
8.	Name and daytime telephone number of person to contact in the United Kingdom	Stephen P McNeeney – (0115) 9552211

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there are more than three inventors, please write the names and addresses of the other inventors on the back of another Patents Form 7/77 and attach it to this form.*

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e) *Once you have filled in the form you must remember to sign and date it.*

Enter the full name, address and postcodes of the inventors in the boxes and underline the surnames

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Patents ADP number *(if you know it)*: 0537220500 1

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Patents ADP number *(if you know it)*: 0537922130 01

Reminder

Have you signed the form?

Patents ADP number *(if you know it)*:

PHARMACEUTICALLY-USEFUL COMPOUNDS

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The invention further relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes to their production.

Background and Prior Art

The endogenous hormone AngII is a linear octapeptide (Asp^1-Arg^2-Val^3-Tyr^4-Ile^5-His^6-Pro^7-Phe^8), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract and the reproductive organs (de Gasparo *et al*, *Pharmacol. Rev.* (2000) **52**, 415-472).

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor. The AT1 receptor is expressed in most organs, and is believed to be

responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, **10**, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al, supra*). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al, supra*).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al, supra*.

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).

However, there remains a need for effective and/or selective AT2 receptor agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent application EP 512 675; international patent applications WO 94/27597, WO 94/02142, WO 95/23792 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074, 5,412,097, 5,520,521, 5,260,285, 5,376,666, 5,252,574, 5,312,820, 5,330,987, 5,166,206, 5,932,575 and 5,240,928. AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

Peptide and non-peptide AT2 receptor agonists, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743, WO 99/26644, WO 98/33813, WO 00/02905 and WO 99/46285; US patent number 5,834,432; and Japanese patent application JP 143695.

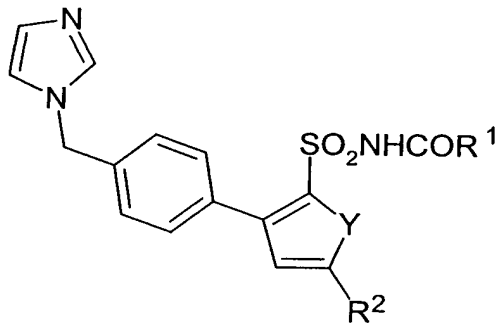
International patent application WO 00/68226 discloses compounds comprising substituted imidazolyl groups, which groups are attached, *via* a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested.

US patent number 5,444,067 discloses compounds comprising a 5,7-dimethyl-2-ethylpyridinoimidazolyl group attached, *via* a methylene bridge, to a phenylthiophene moiety, as AT2 receptor agonists. The use of

unsubstituted imidazole-containing compounds is neither mentioned nor suggested.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,



I

wherein

R^1 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or -CH_2-O-*n*-butyl;

R^2 represents *n*-butyl or *iso*-butyl; and

Y represents –S- or –CH=CH-;

or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to together hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of

a salt with another counter-ion, for example using a suitable ion exchange resin.

Preferred compounds of formula I include those in which:

R^1 represents -O-*n*-butyl;

R^2 represents *iso*-butyl;

Y represents -S-.

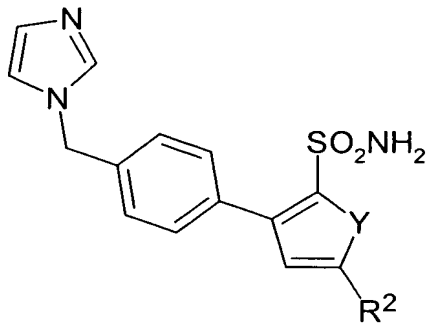
More preferred compounds of the invention include the compound of the example described hereinafter.

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) reaction of a compound of formula II,



II

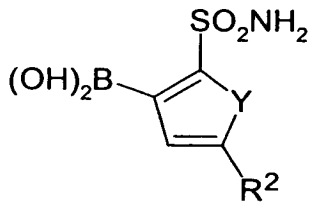
wherein R^2 and Y are as hereinbefore defined with a compound of formula III,

$$R^1C(O)L^1 \qquad \text{III}$$

wherein L^1 represents a suitable leaving group, such as halo (e.g. chloro) and R^1 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. pyrollidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, di-*iso*-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, trifluoromethylbenzene or triethylamine); or

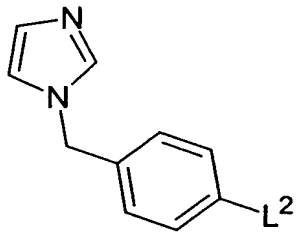
(ii) for compounds of formula I in which R^1 represents $-CH_2$-O-*n*-butyl, coupling of a compound of formula II as hereinbefore defined with *n*-butoxyacetic acid, for example in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole, N,N'-dicyclohexylcarbodiimide, N,N'-disuccinimidyl carbonate, benzotriazole-1-yloxytris(dimethyl-amino)phosphoniumhexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, bromo-tris-pyrrolidino-phosponium hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a suitable base (as mentioned above) and an appropriate solvent (as mentioned above).

Compounds of formula II may be prepared by reaction of a compound of formula IV,



IV

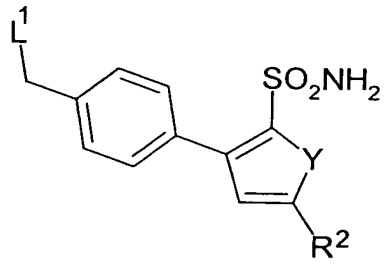
wherein R^2 and Y are as hereinbefore defined, or a N-protected derivative thereof, with a compound of formula V,



V

wherein L^2 represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as $Pd(PPh_3)_4$ or $Pd(OAc)_2$ and a suitable base (e.g. sodium hydroxide, sodium carbonate, cesium carbonate, triethylamine or di-*iso*-propylamine)), as well as a suitable solvent system (e.g. toluene, ethanol, dimethoxymethane, dimethylformamide, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at the reflux temperature of the solvent system that is employed). If a protected version of a compound of formula IV is employed, this reaction may be followed by deprotection of the SO_2NH-group under standard conditions, for example as described hereinafter.

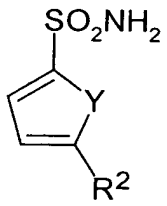
Compounds of formula II may alternatively be prepared by reaction of imidazole with a compound of formula VI,



VI

wherein Y, R^2 and L^1 are as hereinbefore defined, or a N-protected derivative thereof. Compounds of formula II in which Y is –CH=CH- may be prepared in this way for example according, or analogously, to processes described in *inter alia* US patent number 5,312,820. Compounds of formula II in which Y is –S- may be prepared in this way for example according, or analogously, to processes described in *inter alia* UK patent application GB 2281298.

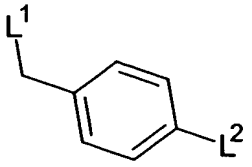
Compounds of formula IV and N-protected derivatives thereof may be prepared by reaction of a compound of formula VII,



VII

wherein R^2 and Y are as hereinbefore defined, or a N-protected derivative thereof, with an appropriate reagent system that will enable the introduction of the $-B(OH)_2$ group into the benzene or thiophene ring system, for example a trialkylborate (e.g. tri-*iso*-propylborate), which reaction may be carried out, for example, at low temperature (e.g. -78°C) in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).

Compounds of formula V may be prepared by standard techniques, for example by reaction of imidazole with a compound of formula VIII,



VIII

wherein L^1 and L^2 are as hereinbefore defined, for example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide) and an appropriate organic solvent (e.g. DMSO).

Compounds of formula VI are known in the art. For example, they may be prepared according, or analogously, to processes described in *inter alia* US patent number 5,312,820 or UK patent application GB 2281298.

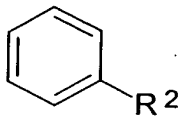
Compounds of formula VII in which Y is –S-, and N-protected derivatives thereof, may be prepared by reaction of thiophene-2-sulfonic acid amide (or a N-protected derivative thereof), with a compound of formula IX,

$$R^2L^3 \qquad \text{IX}$$

wherein L^3 represents a suitable leaving group (such as toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and R^2 is as hereinbefore defined, for example at below room temperature (e.g. between around -35°C and around -85°C), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

N-protected derivatives of thiophene-2-sulfonic acid amide may be prepared by way of standard techniques, for example from thiophene-2-sulfonyl chloride (e.g. as described hereinafter).

Compounds of formula VII in which Y represents –CH=CH-, and N-protected derivatives thereof, may be prepared by reaction of an appropriate alkylbenzene of formula X,



X

wherein R^2 is as hereinbefore defined with chlorosulphonic acid, followed by reaction of the resultant intermediate with ammonia, or a protected derivative thereof (e.g. *tert*-butylamine), under conditions that are well known to those skilled in the art.

Compounds of formulae III, VIII, IX and X are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido. Suitable protecting groups for sulphonamido include *tert*-butyloxycarbonyl, benzyloxycarbonyl, 2-trimethylsilylethoxycarbonyl (Teoc) or *tert*-butyl.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid or boron trichloride).

Medical and Pharmaceutical Uses

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation and/or mucosa-protective mechanisms.

Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pancreatitis, hepatitis, gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis, hyperacidity, disorders of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases, pneumonitis, pulmonary hypertension and adult respiratory distress syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.

Cardiovascular disorders that may be mentioned include hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, diabetic complications and microvascular dysfunction.

Disorders of the CNS that may be mentioned include cognitive dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke, cerebral bleeding, cerebral embolus and cerebral infarction.

Compounds of the invention may also be useful in the modulation of growth metabolism and proliferation, for example in the treatment of hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, the healing of ulcers, inhibition of adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and hypertrophy.

The compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition in which endogenous production of AngII is deficient, and/or a condition where an increase in the effect of

AngII is desired or required, and/or a condition where AT2 receptors are expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with AT1 receptor antagonists that are known in the art, such as losartan.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention; and

(B) an AT1 receptor antagonist,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of compound of the invention in conjunction with AT1 receptor antagonist, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of the invention and at least one comprises AT1 receptor antagonist, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of the invention and AT1 receptor antagonist).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg per patient.

Individual doses of compounds of the invention may be in the range 1 to 100 mg.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT2 receptor. By compounds which "bind selectively" to the AT2 receptor, we include that the affinity ratio for

the relevant compound (AT2:AT1) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.

The compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

Biological Tests

The following test procedures may be employed.

Test A

Receptor Binding Assay using Rat Liver Membrane AT_1 Receptor

Rat liver membranes were prepared according to the method of Dudley *et al* (*Mol. Pharmacol.* (1990) **38**, 370). Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 4 × 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT_1 receptor were determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]AngII. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]AngII. The

dissociation constant (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM) were determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

Test B

Receptor Binding Assay using Porcine Myometrial Membrane AT_2 Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al* (*Clin. Exp. Pharm. Phys.* (1997) **24**, 309). Any possible interference that may be exhibited by binding of compound to AT_1 receptors was blocked by addition of 1 μM of a selective AT1 inhibitor. Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT_2 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]Ang II. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]Ang II. The dissociation constant (K_d = 0.7 ± 0.1 nM, [L] = 0.057 nM) were determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate .

Test C

Duodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-anaesthetised rats prepared for *in situ* titration of duodenal mucosal alkaline secretion, according to the methodology described by Flemström *et al* in *Am. J. Physiol.* (1982) **243**, G348.

The invention is illustrated by the following example.

Example 1

N-Butyloxycarbonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

(a) *N-tert*-Butylthiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in $CHCl_3$ (200 mL) under N_2 atmosphere and then cooled to 0°C. *tert*-Butylamine (25.9 mL, 0.246 mol) dissolved in $CHCl_3$ (50 mL) was then added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at room temperature and then at reflux for 10 min. Toluene (700 mL) was added and the organic phase was washed with water (3 x 50 mL), dried, and concentrated *in vacuo*. The sub-title product was used without further purification in the next step.

^{1}H NMR δ($CDCl_3$): 7.60(1H, dd, J=1.3, 3.8 Hz), 7.53(1H, dd, J=1.3, 5.0 Hz), 7.02(1H, dd, J=5.0, 3.8 Hz), 5.13(1H, m), 1.24 (9H, m)

^{13}C NMR δ($CDCl_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(b) 5-*iso*-Butyl-*N-tert*-butylthiophene-2-sulfonamide

N-tert-Butylthiophene-2-sulfonamide (10 g, 0.046 mol, see step (a) above) was dissolved in THF (85 mL) under N_2 and then cooled to –78°C. *n*-BuLi

(1.6 M, 76.9 mL, 0.12 mol) was added *via* a syringe. The reaction mixture was stirred at –78°C for 30 min. and then at –40°C for 2 h. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

^{1}H NMR δ($CDCl_3$): 7.43(1H, d, J= 3.6 Hz), 6.67(1H, d, J=3.8 Hz), 4.83(1H, m), 2.67(2H, d, J=7 Hz), 1.88 (1H, m), 1.26(9H, m), 0.93(6H, J=6.6 Hz).
^{13}C NMR δ($CDCl_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(c) 5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid

5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide (10.6 g, 0.039 mol, see step (b) above) was dissolved in THF (165 mL) under N_2 and then cooled to –78°C. *n*-BuLi (1.6 M, 60.19 mL, 0.096 mol) was added *via* a syringe. The reaction mixture was stirred at –20°C for 4 h. The tri-*iso*-propylborate (13.3 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The product was used without further purification.

MS(ESI^+) m/z: 236.8

(d) 1-(4-Bromobenzyl)-1H-imidazole

Dimethyl sulphoxide (20 mL; dried over 4A molecular sieve) was added to potassium hydroxide (2.24 g, 0.04 mol, crushed pellets) and the mixture was stirred for 5 min. Imidazole (0.5718 g, 0.0084 mol) was then added

and the mixture was stirred for 2 h. 4-Bromobenzyl bromide (3.25 g, 0.013 mol) was added and the mixture was cooled briefly and stirred for a further 1 h before water (20 mL) was added. The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $CaCl_2$ and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$:MeOH (30:1) plus 0.05% formic acid as eluent to give the sub-title product (1.275 g, yield: 53%).

^1H NMR δ($CDCl_3$): 7.73(3H, m), 7.28(3H, m), 7.15(1H, m), 5.30(2H, s)

^{13}C NMR δ($CDCl_3$): 136.8, 134.8, 131.5, 129.3, 128.4, 121.5, 118.7, 49.4.

MS(ESI^+) m/z: 236.8

(e) 3-(4-Imidazole-1-ylmethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (200.5 mg, 0.628 mmol, see step (c) above), 1-(4-bromobenzyl)-1H-imidazole (98.8 mg, 0.416mmol, see step (d) above), toluene (15 mL), ethanol (15 mL), NaOH (1.0M, 1.5 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (14.5 mg, 0.125 mmol) were mixed under N_2. The mixture was warmed to reflux for 2 h. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography with chloroform:methanol (20:1) as an eluent to give 113.9mg of the sub-title compound (yield: 63.27%).

IR(pure): 3060, 2996, 1507 cm^{-1}

^1H NMR δ($CDCl_3$): 7.39(1H,s), 7.35(2H, d, J=8.1 Hz), 6.98(2H, d, J=8.1 Hz), 6.96(1H, s), 6.84(H, s), 6.47(H, s), 4.91(2H, s), 3.96(1H,s), 2.72(H, brs), 2.42(2H, d, J=7.1 Hz), 1.64(1H, m), 0.73(9H, s), 0.72(6H, d, J=6.9 Hz)

^{13}C NMR δ($CDCl_3$): 148.6, 142.3, 137.2, 136.2, 135.1, 129.7, 129.4, 128.8, 127.4, 119.2, 54.6, 50.6, 39.2, 30.5, 29.5, 22.1

MS(ESI$^+$) m/z: 431.9 Anal. Calcd. for $C_{22}H_{29}N_3O_2S_2$: C, 58.8; H, 7.0; N, 9.4. Found: C, 58.7.0; H, 6.7; N, 9.1.

(f) 3-(4-Imidazole-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

Trifluoroacetic acid was added (2 mL) to 3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (113 mg, 0.2618 mmol, see step (e) above) and one drop (*ca.* 0.05 mL) of anisole (*ca.* 0.05 mL) was added to the mixture. The reaction mixture was stirred under N_2 atmosphere for 30 h and then evaporated and co-evaporated with acetonitrile until TLC showed that it was pure. The crude product was used directly in the next step without further purification.

^{1}H NMR δ($CDCl_3$): 7.70(1H,s), 7.57(2H, d, J=8.1 Hz), 7.19(2H, d, J=8.1 Hz), 7.10(1H, s), 6.93(H, s), 6.73(H, s), 5.14(2H, s), 2.67(2H, d, J=7.1 Hz), 2.62(H, brs), 1.94(1H, m), 0.97(6H, d, J=6.6 Hz)

^{13}C NMR δ($CDCl_3$): 148.4, 142.9, 137.2, 136.2, 134.6, 129.7, 129.3, 128.8, 127.3, 119.2, 50.6, 39.2, 30.5 22.1

MS(EI$^+$) m/z: 375.9

(g) *N*-Butyloxycarbonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

The crude 3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide from step (f) above was dissolved in pyridine (2 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (40.52 mg, 0.2618 mmol) and butyl chloroformate (363.5 mg, 0.339 mL) were added to the mixture. The mixture was stirred overnight under a N_2 atmosphere at room temperature. Evaporation and co-evaporation with acetonitrile to remove the solvents and purification on column chromatography with 10% MeOH in chloroform as eluent gave the title compound (57.8 mg, 0.1217 mmol) in a 46.5% yield (over the last two steps).

IR(pure): 3555.8, 3120.3, 2955.9, 1694.2, 1268.5 cm^{-1}

^{1}H NMR δ($CDCl_3$): 7.96(1H,s), 7.57(2H, d, J=7.9 Hz), 7.10(2H, d, J=7.9 Hz), 6.89(H, s), 6.85(H, s), 6.74(H, s), 5.16(2H, s), 4.03(2H, t, J=6.6 Hz), 2.71(2H, d, J=7.1 Hz), 1.94(1H, m), 1.51(2H,m), 1.25(2H, m), 0.98(6H, d, J=6.6 Hz), 0.87(3H, t, J=7.4 Hz)

^{13}C NMR δ($CDCl_3$): 152.5, 158.4, 143.9, 136.4, 134.6, 133.0, 129.8, 128.9, 127.3, 125.6, 119.6, 65.9, 51.2, 39.3, 30.6, 30.4, 22.3, 18.9, 13.7

MS(EI^+) m/z: 476.0 Anal. Calcd for $C_{23}H_{29}N_3O_4S_2$ H_2O: C, 56.0; H, 6.3; N, 8.5. Found: C, 56.4; H, 6.2; N, 8.6

Example 2

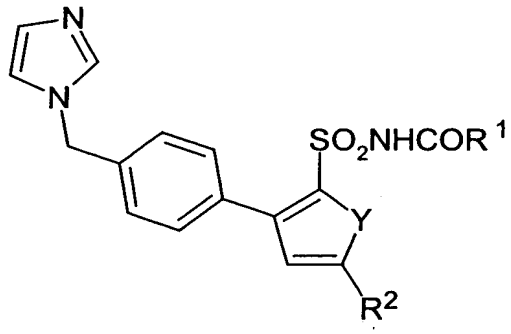
The title compound of Example 1 was tested in Tests A and B above and was found to exhibit an affinity for AT2 receptors of at least Ki = 50 nM and an affinity to AT1 receptors of less than Ki = 1 μM.

Example 3

The title compound of Example 1 was tested in Test C above and was found to stimulate markedly mucosal alkalisation. This effect was blocked by co-administration of the selective AT2 receptor antagonist PD123319 (Sigma Chemical Company).

Claims

1. A compound of formula I,



I

wherein

R^1 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or -CH_2-O-*n*-butyl;

R^2 represents *n*-butyl or *iso*-butyl; and

Y represents –S- or –CH=CH-;

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein R^1 represents -O-*n*-butyl.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^2 represents *iso*-butyl.

4. A compound as claimed in any one of Claims 1 to 3 wherein Y represents -S-.

5. *N*-Butyloxycarbonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide, or a pharmaceutically-acceptable salt thereof.

6. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. A compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

8. A compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

9. A compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which endogenous production of AngII is deficient.

10. A compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which an increase in the effect of AngII is desired or required.

11. A compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

12. The use of a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

13. The use of a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which endogenous production of AngII is deficient.

14. The use of a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which an increase in the effect of AngII is desired or required.

15. The use of a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

16. The use as claimed in any one of Claims 12 to 15, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

17. The use as claimed in Claim 16, wherein the condition is oesophagitis, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatitis, gall bladder disease, multiple organ failure, sepsis, xerostomia, gastritis, gastroparesis, hyperacidity, a disorder of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren's syndrome, inflammatory disorders, asthma, an obstructive lung disease, pneumonitis, pulmonary hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature

retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post baloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer, apoptosis, tumours or hypertrophy.

18. The use as claimed in Claim 17, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

19. A method of treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

21. A kit of parts comprising components:

(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable salt

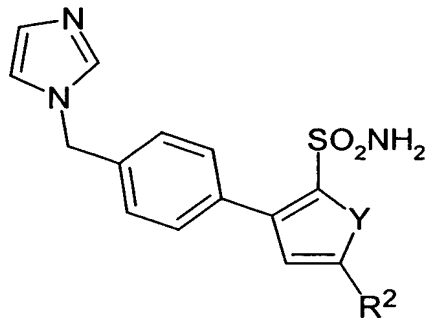
thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

22. A process for the preparation of a compound as defined in any one of Claims 1 to 5, which comprises:

(i) reaction of a compound of formula II,



II

wherein R^2 and Y are as defined in any one of Claims 1 to 5 (as appropriate) with a compound of formula III,

$$R^1C(O)L^1 \qquad \text{III}$$

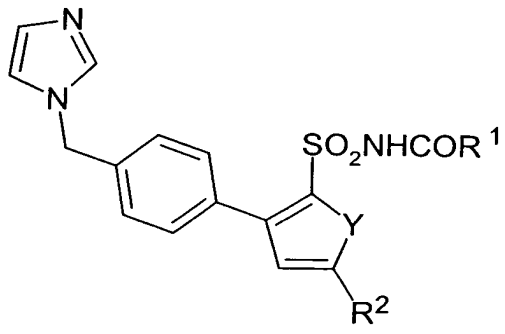
wherein L^1 represents a suitable leaving group and R^1 is as defined in any one of Claims 1 to 5 (as appropriate); or

(ii) for compounds of formula I in which R^1 represents $-CH_2$-O-*n*-butyl, coupling of a compound of formula II as defined above with *n*-butoxyacetic acid.

23. A compound of formula II as defined in Claim 22 or a protected derivative thereof.

ABSTRACT

There is provided a compound of formula I,



I

wherein R^1, R^2 and Y have meanings given in the description, or a pharmaceutically-acceptable salt thereof, which compounds are useful as selective agonists of the AT2 receptor, and thus, in particular, in the treatment of *inter alia* gastrointestinal conditions, such as dyspepsia, IBS and MOF, and cardiovascular disorders.